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(71) Applicant: UNITED STATES OF AMERICA, represented by THE SECRETARY, UNITED STATES DEPARTMENT OF COMMERCE [US/US]; Washington, DC 20231 (US).

(72) Inventors: ROTHMAN, Richard, B. ; 1510 Flora Court, Silver Spring, MD 20910 (US). PERT, Agu ; 20327 Gentle Way, Gaithersburg, MD 20879 (US). RICE, Kenner, C. ; 9007 Kirkdale Road, Bethesda, MD 20817 (US). GREIG, Nigel, Hamilton ; 14415 Long Green Drive, Silver Spring, MD 20906 (US). REID, Audrey, Alice ; 5225 Pooks Hill Road, # 714S, Bethesda, MD 20814 (US). AKUNNE, Hyacinth, Charles, Chi ; 13502 Attleboro Court, #12, Laurel, MD 20708 (US). MELE, Andre ; 3304 Ferndale Street, Kensington, MD 20895 (US). THURKAUF, Andrew ; 6 Foxbridge Village Road, Branford, CT 06405 (US).

(74) Agents: OLIFF, James, A. et al; Oliff & Berridge, P.O Box 19928, Alexandria, VA 22320 (US).

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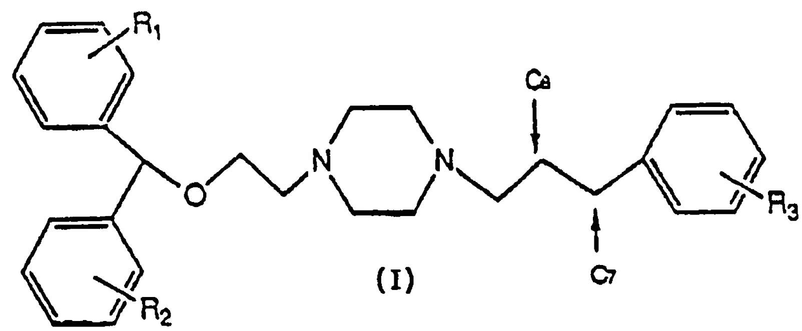

(I)

(57) Abstract

Methods are disclosed for treating cocaine addiction, acute effects of cocaine, and cocaine craving in mammals using a cocaine antagonist of general formula (I). The methods of treatment can counteract cocaine intoxication and prevent relapse into drug use during and after treatment. Preferably, (1-[2-[bis(4-fluorophenyl)-methoxy]ethyl]-4-[3-phenylpropyl]-piperizine is administered in the range of 0.1 mg to 100 mg per kg body weight per day.

* See back of page

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SLOWLY DISSOCIATING (TIGHT BINDING) DOPAMINE, SEROTONIN OR NOREPINEPHRINE REUPTAKE INHIBITORS AS COCAINE, AMPHETAMINE AND PHENCYCLIDINE ANTAGONISTS

BACKGROUND OF THE INVENTION

The abuse of cocaine, amphetamine, phencyclidine (PCP) and similar drugs is a major public health problem in the United States. These highly addictive drugs initially produce euphoria. Often users become psychotic, violent, and suicidally depressed. When such drugs are administered by injection, the users are often exposed to viral infections such as AIDS and hepatitis. Safe and effective means of counteracting drug abuse are needed. The invention disclosed herein provides a means for blocking the acute effects of such drugs. By decreasing or limiting the "high" effect of dosing with euphoria producing drugs, the method of treatment can counteract cocaine intoxication and prevent relapse into drug use during and after treatment. It has been demonstrated that 1-[2[bis(4-fluorophenyl)methoxy]ethyl]-4-[3-phenylpropyl]piperazine (GBR12909) and similar medications act as a cocaine antagonists.

GBR12909 and analogs have been patented [Eur. Pat. Appl. EP 243,903 (Cl. C07D295/08, 04 NOV 1987] as dopamine agonists for the treatment of Parkinsonism, acromegaly and hyperprolactinemia. However, the method of the invention using GBR12909 and analogs thereof as cocaine antagonists had not been known previously.

Clinically effective antidepressant drugs are used to treat cocaine craving. However, the efficacy of this treatment modality is controversial. It has been known that only after weeks of administration of antidepressants can a decrease in craving be observed. Antidepressant drugs previously used include desipramine, imipraine and mazindol. The effectiveness of these drugs for treating abuse is thought to be related to their effectiveness as antidepressants, since the time required to achieve the effect is similar. This treatment of craving differs from the invention, because the GBR12909

blocks the acute effects of cocaine, and the effect occurs immediately after drug administration. Although mazindol, like GBR12909, blocks the reuptake of dopamine, the anti-craving effect of mazindol probably reflects its ability to potently block the reuptake of norepinephrine, a neurotransmitter more associated with affective illness than dopamine.

Another drug, the anti-convulsant carbamazepine, has been reported in open clinical trials involving a small number of patients to be an effective treatment for cocaine craving. It is thought that its mechanism of action involves suppression of kindling. As described above for the antidepressant drugs, this treatment strategy differs from the use of GBR12909 as a cocaine antagonist.

SUMMARY OF THE INVENTION

Although drug treatments for cocaine craving are available, there are currently no drugs available which will effectively block the acute effects of cocaine. We have discovered that (1-[2-[bis(4-fluorophenyl)methoxy]ethyl]-4-[3-phenylpropyl]piperazine, known as GBR12909 acts as a cocaine antagonist in animal models of cocaine abuse. We believe that the ability of GBR12909 to bind tightly to, and dissociate slowly from, the dopamine (DA) reuptake complex, is the underlying mechanism responsible for its cocaine antagonist activity.

The administration of this compound, or compounds which work via the same mechanism, for the treatment of cocaine, amphetamine and PCP abuse in humans was not previously known. For the purposes of this invention, we extend the term "tight binding" to drugs which bind tightly either as a result of strong noncovalent bonds, or as a result of formation of covalent bonds, to the reuptake complex. Although inhibition of DA reuptake is thought to be the major neurochemical mechanism responsible for the addictive properties of cocaine, PCP

and amphetamine, these agents also interact with the reuptake carriers for serotonin and norepinephrine. The treatment of these addictions is also within the scope of the invention wherein treatment effects the DA reuptake complex, since these drugs also bind tightly (reversibly or irreversibly) to the serotonin or norepinephrine reuptake carriers.

GBR12909 is known to be a high affinity blocker of DA reuptake. The data reported demonstrates that GBR12909 binds tightly to the DA reuptake complex after in vivo administration, and can be used to antagonize the effects of cocaine to elevate ECDA levels, a bioassay thought to be highly relevant to the euphoric and addictive effects of cocaine. Data presented supports the use of this agent, or other tight-binding, slowly dissociating, or irreversible, DA reuptake blockers, to antagonize the acute effects of cocaine, amphetamine, and PCP. Moreover, to the extent that inhibition of serotonin or norepinephrine reuptake contributes to the addictive effects of cocaine, amphetamine, and PCP, tight binding reversible, or irreversible ligands, which are not abused by humans, should also prove to be effective antagonists. Although several drugs are already known in use as DA reuptake blockers, the concept for using tight-binding, irreversible or slowly dissociating biogenic amine reuptake blockers as antagonists effecting drug habituation provides a new and useful application of these medicinal compounds.

TABLE 1

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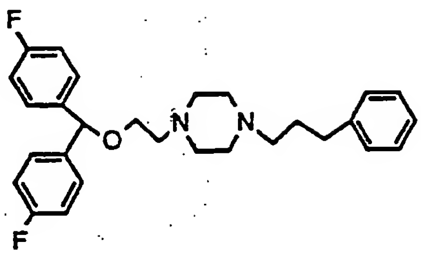

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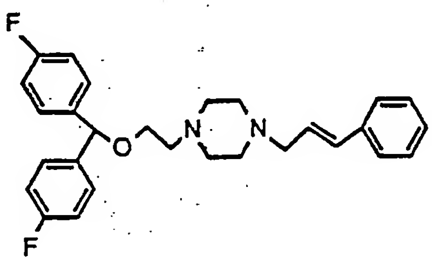

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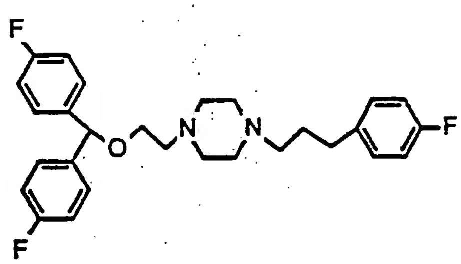

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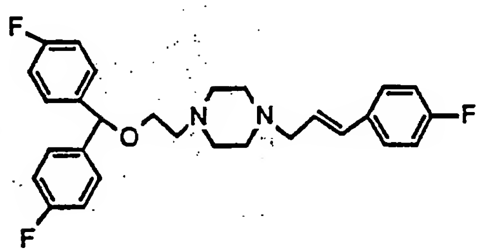

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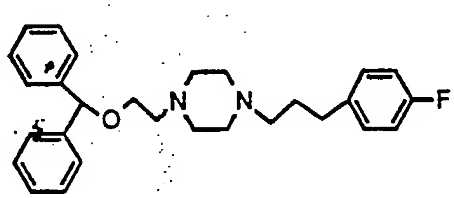

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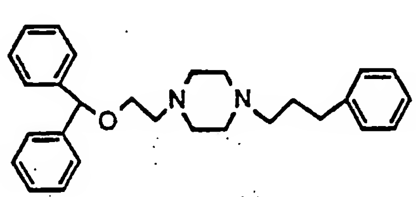

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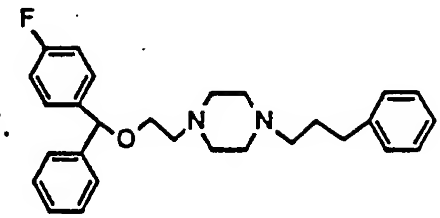

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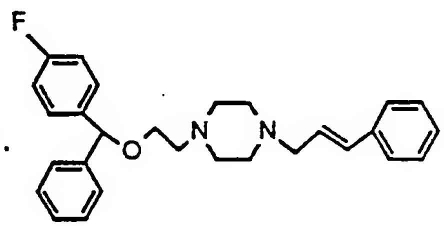

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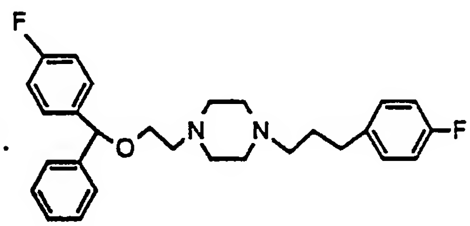

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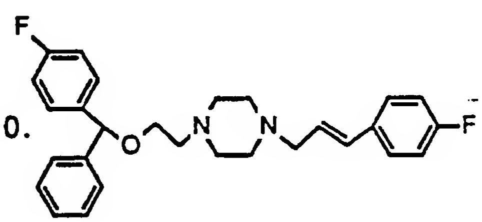

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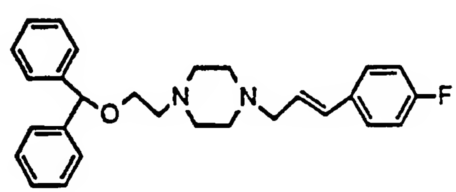

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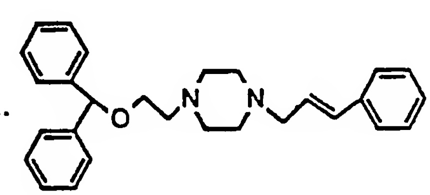
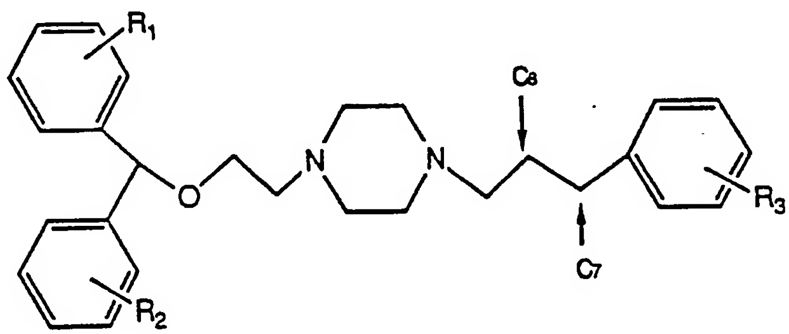


DETAILED DESCRIPTION OF THE INVENTION

Chemistry

A cocaine antagonist is provided by treatment with an effective amount of a compound of the class of substituted 1-[2-(diphenylmethoxy)ethyl]piperazines represented by Formula 1:



Formula 1

wherein each of R_1 and R_2 is independently selected from hydrido, halo, cyano, carboxyl, nitro, hydroxyl, alkoxyl, amino, alkylamino, alkylthio, mercapto, haloalkyl, and linear or branched alkyl groups of from one to about twenty carbon atoms, and wherein R_3 selected from hydrido, halo, cyano, carboxyl, nitro, hydroxyl, alkoxyl, haloalkyl, amino, alkylamino, alkylthio, mercapto and linear or branched alkyl groups of from one to about ten carbon atoms, and wherein the atomic linkage from the carbon atoms labelled C7 and C8 is selected from either single (alkyl), double (alkenyl) or triple (alkynl) bonds; or a pharmaceutically acceptable salt thereof.

A preferred class of compounds within Formula I are those wherein each of R_1 and R_2 is independently

selected from hydrido, halo, alkyl, haloalkyl, cyano, hydroxyl or alkoxyl; wherein R_3 is selected from hydrido, halo, alkyl, haloalkyl, hydroxy, alkoxy, or cyano; and wherein the atomic linkage from the carbon atoms labelled C7 and C8 is selected from either single (alkyl) or double (alkenyl) bonds.

The term hydrido denotes a single hydrogen atom (H) which may be attached, for example, to a carbon atom or to a nitrogen atom to form a primary or secondary amino group. Where the term 'alkyl' is used, either alone or within other terms such as 'haloalkyl' or 'alkylamino', the term 'alkyl' embraces linear or branched radicals having one to about ten carbon atoms. Preferred alkyl radicals are "lower alkyl" radicals having from one to about five carbon atoms. The term "haloalkyl" embraces radicals wherein one or more of the alkyl carbon atoms is substituted with one or more halogens atoms, preferably selected from fluoro, chloro and bromo. Specifically embraced by the term 'haloalkyl' are monohaloalkyl, dihaloalkyl and polyhaloalkyl groups. Examples of a polyhaloalkyl are trifluoromethyl, 2,2,2-trifluoroethyl and perfluoroethyl. The term 'alkenyl' embraces an electronic configuration between two atoms which is referred to, by those skilled in the art, as a double carbon-carbon bond possessing SP^2 hybridization. The term 'alkynyl' embraces an electronic configuration between two atoms which is referred to, by those skilled in the art, as a triple carbon-carbon bond possessing SP hybridization. The term 'alkoxy' embraces linear or branched oxy-containing radicals having alkyl portions of from one to about ten carbon atoms, such as methoxy group. The alkoxy radicals may be further substituted with one or more halo atoms, such as fluoro, chloro or bromo to provide haloalkoxy groups. The term 'alkylamino' embraces linear or branched nitrogen containing radicals where the nitrogen atom may be substituted with from one to three alkyl radicals of from

one to about ten carbon atoms, such as N-methylamino and N,N-dimethylamino.

Specific examples of alkyl groups are methyl, ethyl, propyl, isopropyl, n-butyl, isobutyl, tert-butyl, sec-butyl, neopentyl and n-pentyl.

Included within the family of compounds of Formula I are the tautomeric forms of the described compounds, isomeric forms such as diastereomers, and the pharmaceutically acceptable salts thereof. Examples of acids which may be employed to form pharmaceutically acceptable acid addition salts include such inorganic acids as hydrochloric acid, sulphuric acid and phosphoric acid and such organic acids as maleic acid, succinic acid and citric acid.

Table 1 describes a list of 12 specific compounds of most interest within Formula I.

Biological Evaluation

For meeting the purpose of this invention to provide a means of preventing the psychological "high" usually experienced after dosing with cocaine, amphetamine, phencyclidine and similar agents, the compounds of the invention can be used in the form of pro-drugs having attached to the active component easily hydrolyzable substituents such as amine, amide, carboxyl, benzyl groups and other substituents known in the pharmaceutical industry.

Cocaine, a major drug of abuse, is thought to produce its effects primarily by inhibiting the reuptake of biogenic amines. Although cocaine inhibits reuptake of norepinephrine, and serotonin, its ability to inhibit reuptake of dopamine (DA) is thought to be the main neurochemical mechanism responsible for its addictive and euphorogenic properties. The role that inhibition of serotonin and norepinephrine reuptake plays is not well defined.

Several lines of data support the DA hypothesis: 1) a role of dopaminergic systems as neurochem-

ical mediators of reward; 2) a correlation between the potency of cocaine-like drugs to inhibit DA reuptake and their potency as self-administered agents in animals. However, not all DA reuptake inhibitors are abused by humans. Mazindol and nomifensine, which are more potent inhibitors of DA reuptake in vitro than cocaine, are not abused and are clinically effective antidepressants in man. Moreover, benztropine, a drug widely prescribed for treatment of Parkinson's disease and for treatment of extrapyramidal side effects resulting from administration of antipsychotic drugs, is also a potent inhibitor of DA reuptake which is not abused. To reflect these differences, we term DA reuptake blockers abused by humans "type 1," and those not abused "type 2." We include cocaine, amphetamine, amphetamine-like drugs, and phenycyclidine and phencyclidine-like drugs as type 1 agents.

Although the reason why type 1 reuptake blockers are abused, and type 2 reuptake blockers are not, is not fully understood at this time, the scientific literature fully supports the hypothesis that an interaction with the DA reuptake complex is crucial. Thus amphetamine must be transported into the dopaminergic nerve terminal via the reuptake complex in order to release intracellular DA. Similarly, if cocaine has amphetamine-like releasing properties, which is not fully established, it too would have to interact with the reuptake complex in order to be transported into the dopaminergic nerve terminal. Moreover, to the extent that the psychotomimetic effects of PCP are due to inhibition of DA reuptake, an interaction with the DA reuptake complex would also play a role in the actions of this drug.

Although inhibition of DA reuptake in vitro does not predict abuse liability in humans, available data suggests that the ability of an agent to elevate extracellular levels of DA (ECDA) in vivo does. For example, cocaine, PCP, and amphetamine all produce large

elevations in ECDA levels as measured by the technique of in vivo microdialysis. In contrast, type 2 DA reuptake blockers such as nomifensine and benztropine are reported to produce much lower and inconsistent elevations of ECDA levels.

It is shown that, defining of ECDA as the dependent variable, which does not specify a mechanism of action, type 1 and 2 DA reuptake inhibitors are full and partial agonists, respectively. That is type 1 agents produce a large elevation of ECDA, and type 2 agents produce much lower levels of ECDA. A direct prediction of this hypothesis is that occupation of the reuptake complex by a type 2 DA reuptake blocker should attenuate the effects of cocaine, and potentially be useful in humans as antagonists of type 1 agents. However, a competitive antagonist would be of limited use, since a person would simply self-administer more of the type 1 agent, overcoming the inhibition, and increasing the risk of peripheral side effects such as cardiac arrthymias. On the other hand, administration of a tight-binding, slowly dissociating type 2 reuptake inhibitor should produce an insurmountable (noncompetitive) inhibition over the time period which it remains bound to the reuptake complex.

GBR12909, a preferred compound, is a potent and slowly dissociating DA reuptake inhibitor which does not produce large elevations in ECDA, as exemplified by:

(1) administration of GBR12909 to rats produces a dose-dependent, wash-resistant inhibition of [^{3}H]cocaine and [^{3}H]GBR12935 1-[2-(diphenylmethoxy)ethyl]-4-(3-phenylpropyl)piperazine binding to the DA-reuptake complex assayed in vitro striatal membranes, indicative of tight-binding.

(2) administration of GBR12909 to rats antagonized the ability of cocaine to elevate ECDA levels in vivo.

Example 1: Rats were injected (i.p.) with

doses of GBR12909. They were sacrificed 60 min. later. Caudates were dissected out and frozen at -70°C. On the day of assay, membranes were prepared. Briefly, caudates were homogenized with a polytron in ice-cold 55.2 mM sodium phosphate buffer, pH 7.4. The homogenate was centrifuged, the pellets were resuspended in ice-cold buffer, and then recentrifuged. The pellets were then resuspended in ice-cold 25 mM sodium phosphate buffer (pH 7.4) for the [^{3}H]cocaine binding assay. The results, shown in Figure 1, demonstrated a dose-dependent psuedo-irreversible inhibition of [^{3}H]cocaine binding.

Example 2: Rats were injected (i.p.) with doses of GBR12909. They were sacrificed 60 min. later. Caudates were dissected out and frozen at -70°C. On the day of assay, membranes were prepared. Briefly, caudates were homogenized with a polytron in ice-cold 55.2 mM sodium phosphate buffer, pH 7.4. The homogenate was centrifuged, the pellets were resuspended in ice-cold buffer, and then recentrifuged. The pellets were then resuspended in ice-cold buffer (pH 7.4) for the [^{3}H]GBR12935 (2 nM) binding assay. The results, shown in Figure 2, demonstrated a dose-dependent psuedoirreversible inhibition of [^{3}H]GBR12935 binding, indicating persistent occupation of the DA reuptake complex. Additional experiments demonstrated that the wash-resistant inhibition was primarily due to a decrease in the number of [^{3}H]GBR12935 binding sites. Other experiments demonstrated that this effect persisted even after washing the membranes six times by centrifugation. The results of experiments 1 and 2 support the hypothesis that GBR12909 binds so tightly to the DA reuptake complex in vivo that it continues to occupy it in vitro. These results are consistent with reports in the literature that GBR12909 dissociates very slowly once it is bound to the DA reuptake complex.

Example 3: Rats were anesthesized with chloryl hydrate, and placed in the microdialysis apparatus. The

injection of 25 mg/kg of GBR12909 produced a stable but low (about 200%) increase in the ECDA levels. Cocaine (0.1, 1.0 and 10.0 mM) was administered through the probe, causing an additional increase in the ECDA level, which returned within 20 min to the preexisting base-line. The increase in the ECDA level produced by cocaine was quantitated as the difference: ECDA (plus cocaine) - ECDA (minus cocaine). The effect of GBR12909 (25 mg/kg and 100 mg/kg) on the effect of cocaine is shown in Figure 3. The results indicated a highly significant attenuation of the ability of cocaine to elevate ECDA levels. Moreover, although the high dose of GBR12909 used (25 mg/kg) was sufficient to completely occupy over 70% of the reuptake binding sites, only a small increase in ECDA levels was observed.

Administration of compounds within Formula I to humans can be by any technique capable of introducing the compounds into the bloodstream of a human patient, including oral administration, and by intraveneous, intramuscular and subcutaneous injections.

Compounds indicated by prophylactic therapy will preferably be administered in a daily dose generally in the range of 0.1 mg to 100 mg per kilogram of body weight per day. A more preferred dosage will be in the range of 1.0 to 50 mg per kilogram of body weight. A suitable dose can be administered in suitable sub-doses per day.

The active compound is usually administered in a pharmaceutically acceptable formulation, although in some acute-care situations a compound of Formula I may be administered alone. Such formulations may comprise the active compound with one or more pharmaceutically acceptable carriers or diluents. Other therapeutic agents may also be present in the formulation. A pharmaceutically acceptable carrier or diluent provides an appropriate vehicle for delivery of the active compound without undesirable side effects. Delivery of the active compound in

such formulations may be by various routes such as oral, nasal, buccal or sublingual, or by parenteral administration such as subcutaneous, intramuscular, intravenous or intradermal routes. Delivery of the active compound may also be through the use of controlled release formulations in subcutaneous implants.

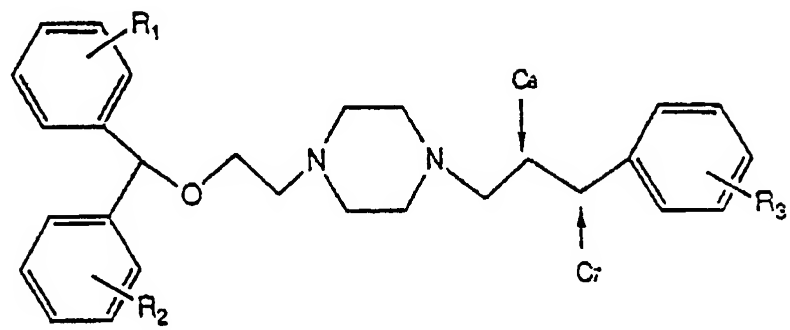
Formulations for oral administration may be in the form of capsules containing the active compound dispersed in a binder such as gelatin or hydroxypropylmethyl cellulose, together with one or more of a lubricant, preservative, surface acting or dispersing agent. Such capsules or tablets may contain controlled release formulation as may be provided in a disposition of active compound in hydroxypropylmethyl cellulose.

Formulations for parental administration may be in the form of aqueous or non-aqueous isotonic sterile injection solutions or suspensions. These solutions or suspensions may be prepared from sterile powders or granules having one or more of the carriers or diluents mentioned for use in the formulations for oral administration.

Although this invention has been described with respect to specific embodiments, the details of these embodiments are not to be construed as limitations. Various equivalents, changes and modifications may be made without departing from the spirit or scope of this invention, and it is understood that such equivalent embodiments are part of this invention. Dosage in mammals is 0.1 - 100 mg/kg and for adult primates, a dose of 0.1 to 1 gm per day is a preferred dosage range.

WHAT IS CLAIMED IS:

1. A method of treating and controlling cocaine addiction and the acute effects of cocaine in mammals, which method comprises administration of a craving inhibiting effective amount of a compound of Formula I:



Formula 1

wherein each of R_1 and R_2 is independently selected from hydrido, halo, cyano, carboxyl, nitro, hydroxyl, alkoxyl, amino, monoalkylamino, dialkylamino, alkylthio, mercapto, haloakyl, and linear or branched alkyl groups of from one to about twenty carbon atoms, and wherein R_3 is selected from hydrido, halo, cyano, carboxyl, nitro, hydroxyl, alkoxyl, amino, alkylamino, alkylthio, mercapto and linear or branched alkyl groups of from one to about ten carbon atoms, and wherein the atomic linkage from the carbon atoms labelled C7 and C8 is selected from either single (alkyl) double (alkenyl) or triple (alkynyl) bonds; or a pharmaceutically acceptable salt thereof.

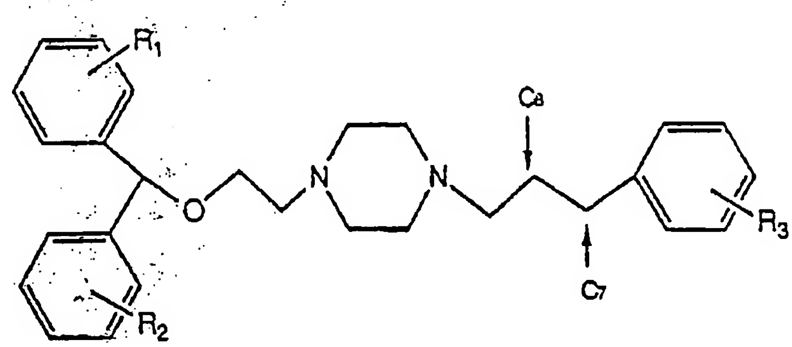
2. The method of Claim 1, wherein each of R_1 and R_2 is independently selected from hydrido, halo, alkyl, haloalkyl, cyano, hydroxyl or alkoxyl; wherein R_3 is selected from hydrido, halo, alkyl, alkenyl, halo,

haloalkyl, hydroxyl, alkoxy, nitro, cyano, thio, mercapto, amino, alkylamino, and wherein the atomic linkage from the carbon atoms labelled C7 and C8 is selected from either single (alkyl), double (alkenyl) or triple (alkynyl) bonds.

3. The method of Claim 2, wherein each of R_1 and R_2 is independently selected from hydrido or halo, wherein R_3 is selected from hydrido or halo, and wherein the atomic linkage from the carbon atoms labelled C7 and C8 is selected from either single (alkyl) or double (alkenyl).

4. The method of Claim 1, using 1-[2-[bis(4-fluorophenyl)methoxy]ethyl]-4-(3-phenylpropyl)piperazine, having the chemical formula corresponding to Compound 1 in Table 1; or a pharmaceutically acceptable salt thereof.

5. A method to treat and control cocaine addiction, acute effects of cocaine, and cocaine craving in mammals, which method comprises treating a mammal afflicted with addiction to cocaine, acute effects of cocaine, or cocaine craving with an effective amount of a pharmaceutical composition comprising a therapeutically effective amount of a compound and a pharmaceutically-acceptable carrier or diluent, said compound selected from a family of compounds of the formula



Formula 1

wherein each of R_1 and R_2 is independently selected from hydrido, halo, cyano, carboxyl, nitro, hydroxyl, alkoxyl, amino, monoalkylamino, dialkylamino, alkylthio, mercapto, haloakyl, and linear or branched alkyl groups of from one to about twenty carbon atoms, and wherein R_3 is selected from hydrido, halo, cyano, carboxyl, nitro, hydroxyl, alkoxyl, amino, alkylamino, alkylthio, mercapto and linear or branched alkyl groups of from one to about ten carbon atoms, and wherein the atomic linkage from the carbon atoms labelled C7 and C8 is selected from either single (alkyl), double (alkenyl) or triple (alkynyl) bonds; or a pharmaceutically acceptable salt thereof.

6. The method of Claim 5, wherein each of R_1 and R_2 is independently selected from hydrido, halo, alkyl, haloalkyl, cyano, hydroxyl or alkoxyl; wherein R_3 is selected from hydrido, halo, alkyl, alkenyl, halo, haloalkyl, hydroxy, alkoxy, nitro, cyano, thio, mercapto, amino, alkylamino, and wherein the atomic linkage from the carbon atoms labelled C7 and C8 is selected from either single (alkyl), double (alkenyl) or triple (alkynyl) bonds.

7. The method of Claim 6, wherein each of R_1 and R_2 is independently selected from hydrido or halo, wherein R_3 is selected from hydrido or halo, and wherein the atomic linkage from the carbon atoms labelled C7 and C8 is selected from either single (alkyl) or double (alkenyl).

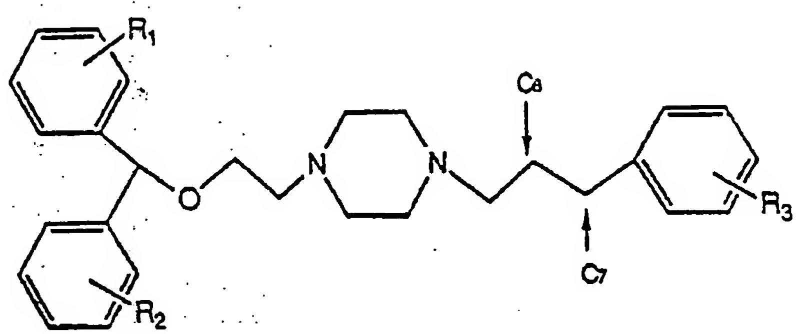
8. The method of Claim 5, using 1-[2-[bis(4-fluorophenyl)methoxy]ethyl]-4-(3-phenylpropyl)piperazine, having the chemical formula corresponding to Compound 1 in Table 1, or a pharmaceutically acceptable salt thereof.

9. The method of Claim 1, wherein the compound is administered orally, intraveneously, intramuscularly or subcutaneously.

10. The method of Claim 5, wherein the compound is administered orally, intravenously, intramuscularly,

or subcutaneously.

11. The use of a compound of Formula I:



Formula 1

wherein each of R_1 and R_2 is independently selected from hydrido, halo, cyano, carboxyl, nitro, hydroxyl, alkoxyl, amino, monoalkylamino, dialkylamino, alkylthio, mercapto, haloakyl, and linear or branched alkyl groups of from one to about twenty carbon atoms, and wherein R_3 is selected from hydrido, halo, cyano, carboxyl, nitro, hydroxyl, alkoxyl, amino, alkylamino, alkylthio, mercapto and linear or branched alkyl groups of from one to about ten carbon atoms, and wherein the atomic linkage from the carbon atoms labelled C7 and C8 is selected from either single (alkyl) double (alkenyl) or triple (alkynyl) bonds; or a pharmaceutically acceptable salt thereof, for treating and controlling cocaine addiction and the acute effects of cocaine in mammals.

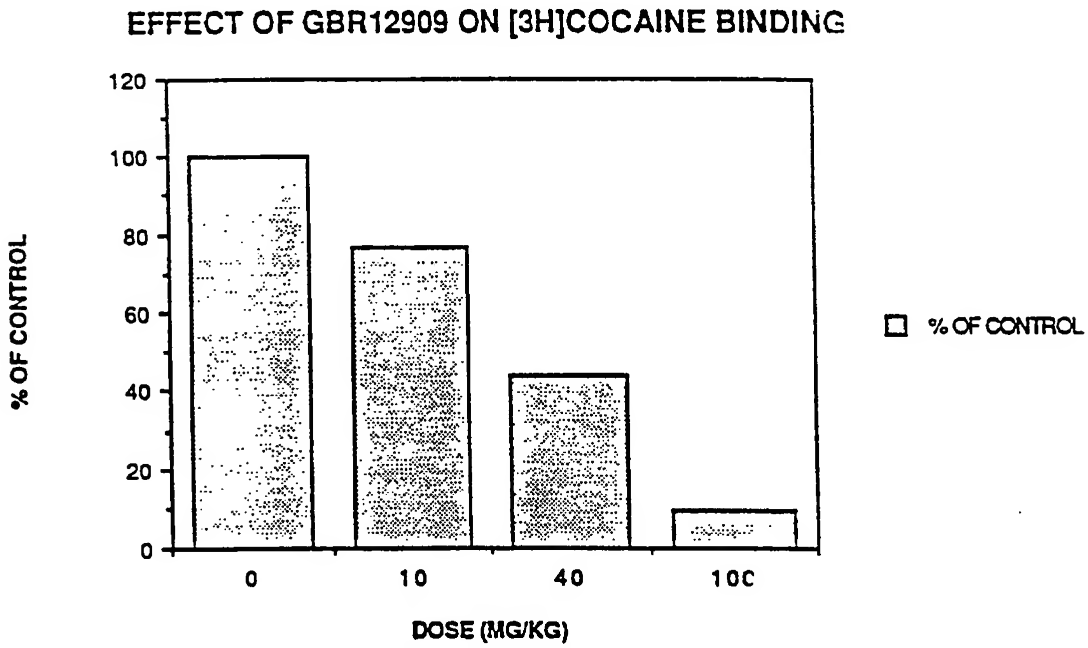
12. The use of Claim 11, wherein each of R_1 and R_2 is independently selected from hydrido, halo, alkyl, haloalkyl, cyano, hydroxyl or alkoxyl; wherein R_3 is selected from hydrido, halo, alkyl, alkenyl, halo, haloalkyl, hydroxyl, alkoxy, nitro, cyano, thio, mercapto, amino, alkylamino, and wherein the atomic

linkage from the carbon atoms labelled C7 and C8 is selected from either single (alkyl), double (alkenyl) or triple (alkynyl) bonds.

13. The use of Claim 12, wherein each of R_1 and R_2 is independently selected from hydrido or halo, wherein R_3 is selected from hydrido or halo, and wherein the atomic linkage from the carbon atoms labelled C7 and C8 is selected from either single (alkyl) or double (alkenyl).

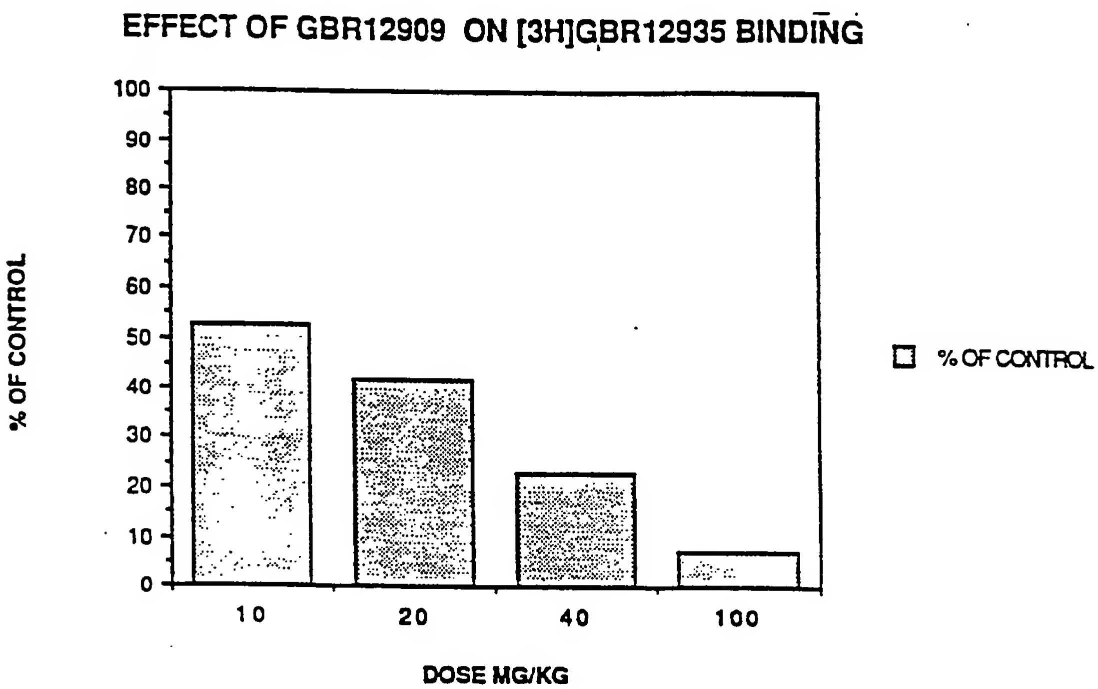
14. The use of Claim 11, using 1-[2-[bis(4-fluorophenyl)methoxy]ethyl]-4-(3-phenylpropyl)piperazine, having the chemical formula corresponding to Compound 1 in Table 1; or a pharmaceutically acceptable salt thereof.

FIGURE 1: EFFECT OF GBR12909 ON [^{3}H]COCAINE BINDING



Each point was the mean of four experiments which differed by less than 10 %.

FIGURE 2: EFFECT OF GBR12909 ON [^{3}H]GBR12935 BINDING



Each point was the mean of four experiments which differed by less than 10 %.

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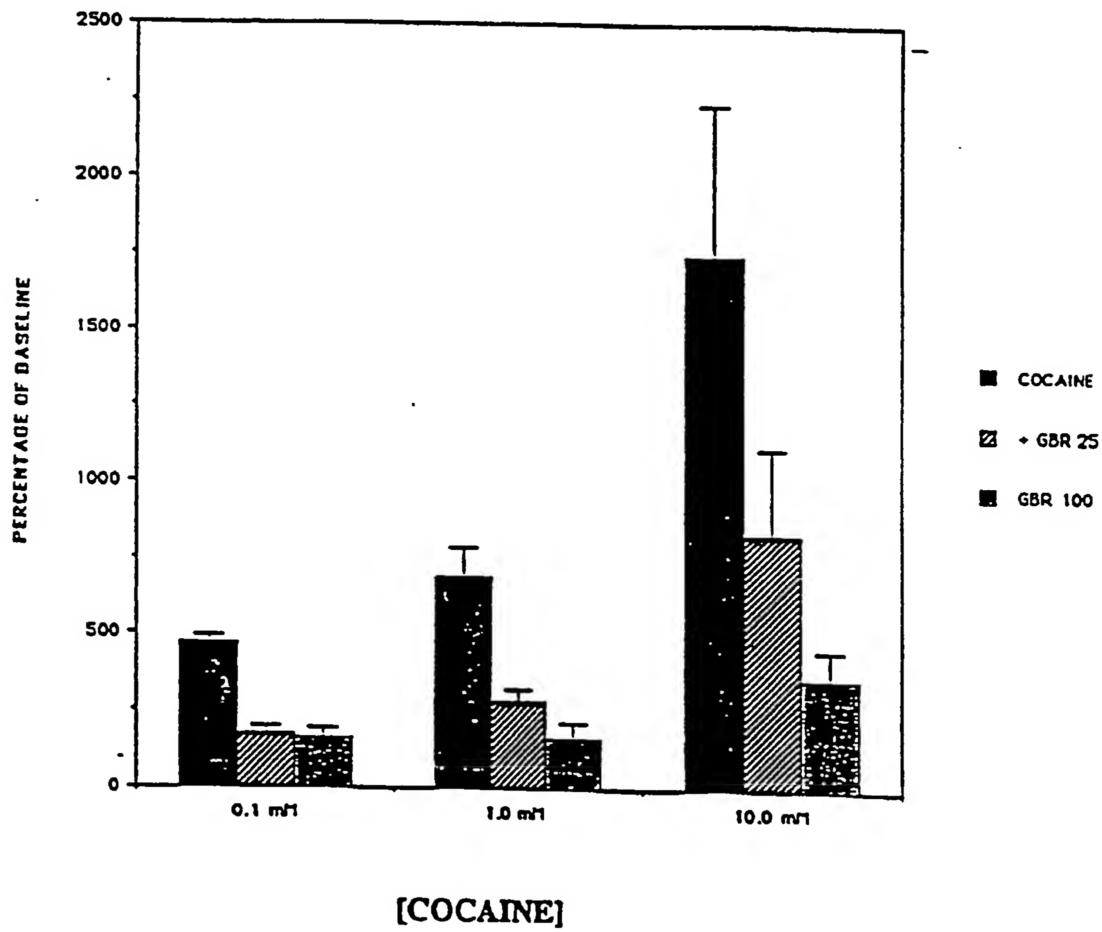
FIGURE 3: GBR12909 BLOCKS COCAINE-INDUCED ELEVATIONS OF EXTRACELLULAR DOPAMINE



Each point is the mean±SEM (n=4-5).

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